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Review article

Clinical utility of the polygenic LDL-C SNP score in familial hypercholesterolemia

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ABSTRACT

Mutations in any of three genes (*LDLR*, *APOB* and *PCSK9*) are known to cause autosomal dominant FH, but a mutation can be found in only ~40% of patients with a clinical diagnosis of FH. In the remainder, a polygenic aetiology may be the cause of the phenotype, due to the co-inheritance of common LDL-C raising variants. In 2013, we reported the development of a 12-SNP LDL-C "SNP-Score" based on common variants identified as LDL-C raising from genome wide association consortium studies, and have confirmed the validity of this score in samples of no-mutation FH adults and children from more than six countries with European-Caucasian populations. In more than 80% of those with a clinical diagnosis of FH but with no detectable mutation in *LDLR/APOB/PCSK9*, the polygenic explanation is the most likely for their hypercholesterolaemia. Those with a low score (in the bottom two deciles) may have a mutation in a novel gene, and further research including whole exome or whole genome sequencing is warranted. Only in families where the index case has a monogenic cause should cascade testing be carried out, using DNA tests for an unambiguous identification of affected relatives. The clinical utility of the polygenic explanation is that it supports a more conservative (less aggressive) treatment care pathway for those with no mutation. The ability to distinguish those with a clinical diagnosis of FH who have a monogenic or a polygenic cause of their hypercholesterolaemia is a paradigm example of the use of genomic information to inform Precision Medicine using lipid lowering agents with different efficacy and costs.

1. Introduction

A clinical diagnosis of familial hypercholesterolemia (FH) can be made using any one of several different published criteria. Across Europe, the most widely used is the Dutch Lipid Clinic Network (DLCN) criteria [1], which use a point system based on patient's cholesterol levels, personal and family history of premature coronary heart disease (CHD), physical examination and the presence of a detected mutation. Those with a score over 8 are given the diagnosis of Definite FH (DFH), those with a score between 6 and 8 the diagnosis of Probable FH, between 3 and 5 the diagnosis of Possible FH, while a score of below 3 is not FH. The criteria have been modified by clinicians in Wales to take into account that an elevated triglyceride level in a suspected FH patient makes it less likely that the patient has monogenic FH [2], which is supported by findings in a lipid clinic in England [3]. In the UK, the National Institute for Health and Care Excellence (NICE) guideline recommends use of the Simon Broome criteria [4]. These criteria include raised cholesterol levels, physical stigmata e.g. tendon xanthomata or an evidence of these signs in first- or second-degree relatives, and having a family history of premature coronary artery disease. A definite diagnosis of FH is made if a patient has elevated cholesterol levels and tendon xanthomata or a disease causing mutation is found. A possible diagnosis of FH is made if the patient has only high levels of cholesterol and a family history of hypercholesterolemia or premature CHD. Finally, the MedPed criteria are used for diagnosis of probable FH in the US and are mainly based on total cholesterol and LDL-C cut offs stratified by age and family history.

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The cut offs are different in individuals with first, second and third degree relatives with FH [5].

In the majority of cases, a single mutation in one of three genes (*LDLR*, *APOB* or *PCSK9*) causes autosomal dominant FH, with a single deletion variant in *APOE* also reported to cause the FH phenotype in a few families [6]. In diagnostic laboratories, a mutation in one of the three genes can be found in 60–80% of patients with a clinical diagnosis of definite FH but only in about 25–30% of patients with possible FH (PFH) [7]. In those mutation positive families, cascade testing (CT) using the family mutation for unambiguous identification of FH relatives is recommended by all recent published guidelines (e.g. Refs. [1,8,9]), with identified subjects treated with high intensity lipid lowering therapies to reduce their very considerable risk of early CHD. CT has been shown to be a feasible and highly cost-effective strategy in many countries (e.g. Refs. [10,11]). However, this leaves a diagnostic problem in patients with no causative mutation, who have a strong possibility of a polygenic cause for their FH [12].

2. Development of the LDL-C SNP-Score

In 2010, the Global Lipids Genetics Consortium (GLGC) meta-analysis identified over 100 loci where common variants influence LDL-C levels [13]. Thus, we hypothesised that in patients where no mutation can be found, the LDL-C and total cholesterol level is raised above the FH diagnostic cut-off by having inherited a greater-than-average number of these common cholesterol-raising variants with modest effect. To test this, we selected 12 key single nucleotide polymorphisms (SNPs) with common variants that raise LDL-C by the largest amount. Using these, we generated an LDL-C "SNP-Score" by summing the number of raising alleles an individual carries, and improved the precision of the score by "weighting" the carriage of each SNP by the size of its effect (Table 1). In a sample of no-mutation FH patients from the UK (FH/M−), we showed that the mean weighted score was significantly higher than in a group of ~3000 healthy UK men and women from the Whitehall II study (WHII), and confirmed this effect in a sample of FH/M-patients from Belgium [12]. The decile SNP-Score cut-offs are shown in Table 2. In the FH/M-group, 52% had a score that fell within the range observed in the top three deciles of the WHII weighted LDL-C gene score distribution, and only 11% fell within the range observed in the lowest three deciles. We estimated that in more than 80% of those with a clinical diagnosis of autosomal dominant FH but with no detectable mutation in *LDLR/APOB/PCSK9*, the polygenic explanation is the most likely cause of their hypercholesterolaemia. In the remainder, a mutation in a novel gene may be present [14,15]. We proposed that only those with a monogenic cause for their phenotype be given the diagnosis of FH, and the remainder be termed "Polygenic Hypercholesterolaemia". In this group, cascade testing will be less cost effective, since, as compared to the 50% of mutation carriers seen in first degree relatives of monogenic families, only ~30% of relatives are likely to have LDL-C elevated above the diagnostic threshold, as was reported in the UK Cascade Testing Project [16].

Table 1
Global Lipid Genetic Consortium [10] 12 SNP LDL-C Gene Score, showing the LDL-C-raising allele and the published raising effect (in mmol/l).

CHR	SNP	Gene	Minor[a]	Common[a]	GLGC weight
1	rs2479409	*PCSK9*	**G**	A	0.052
1	**rs629301**	***CELSR2***	G	**T**	0.15
2	**rs1367117**	***APOB***	**A**	G	0.10
2	**rs4299376**	***ABCG8***	**G**	T	0.071
6	rs1564348	*SLC22A1*	C	**T**	0.014
6	rs1800562	*HFE*	A	**G**	0.057
6	rs3757354	*MYLIP*	T	**C**	0.037
11	rs11220462	*ST3GAL4*	**A**	G	0.050
14	rs8017377	*KIAA1305*	**A**	G	0.029
19	**rs6511720**	***LDL-R***	T	**G**	0.18
19	**rs429358**	***APOE***	C	T	
19	**rs7412**	***APOE***	T	C	
		ε2ε2			−0.9
		ε2ε3			−0.4
		ε2ε4			−0.2
		ε3ε3			0
		ε3ε4			0.1
		ε4ε4			0.2

GLGC weights from Ref. [10] and *APOE* weights were based on haplotypic effects taken from [42].
[a] Risk alleles (LDL-C-raising) are indicated in bold. rs numbers and gene symbols in bold indicate the 6-SNPs used in [15].

Table 2
Mean (SD) of weighted LDL-C 12 SNPs score deciles range as calculated in the WHII study of 3000 healthy UK men and women.

Score deciles	Mean (SD)	Min and max
1	0.43 (0.14)	−0.5–0.58
2	0.66 (0.04)	0.58–0.73
3	0.77 (0.03)	0.73–0.81
4	0.85 (0.02)	0.81–0.88
5	0.91 (0.02)	0.88–0.93
6	0.96 (0.01)	0.94–0.98
7	1.00 (0.01)	0.98–1.02
8	1.05 (0.02)	1.02–1.08
9	1.12 (0.02)	1.08–1.16
10	1.23 (0.06)	1.16–1.46

It is interesting to note in Fig. 1 that the mean weighted SNP-Score in the FH/M+ group is intermediate between the heathy subjects and the FH/M-group. This suggests that, even in those with an identified FH-causing mutation, a polygenic contribution to their phenotypes is occurring. The additional polygenic contribution (with also contribution from environmental factors such as diet) could potentially explain some of the variation in the LDL-C concentrations seen among the family members of an FH patient. In different relatives, the LDL-C levels seen will be determined by the combined contribution of the single mutation of large effect *plus* the contribution of the number of LDL-C-raising alleles inherited, which will of course differ between family members, since the genes are on different chromosomes and will segregate independently.

3. Can the LDL-C SNP score be improved?

It is unlikely that there are additional common SNPs in the genome that will outrank the 12 chosen for the SNP-Score, since any common SNPs with larger effects would have been detected by the size of the datasets currently available. However, it may be possible to improve the performance of the SNP-Score by including additional SNPs previously identified by the GLGC meta-analysis as influencing LDL-C (Supplementary Table 3 in Ref. [17]). In the 2013 analysis, to maintain a high specificity for LDL-C, SNPs were selected with a major effect only on LDL-C and not on another lipid trait. To see if the SNP-Score could be improved, other SNPs were included, and also lipid traits other than LDL-C (e.g. *CETP*). However, addition of 21 LDL-C-raising SNPs did not significantly improve the ability of the SNP-Score to discriminate between FH/M− and healthy subjects [17]. Following this, the sequential removal of SNPs of smaller effects and/or lower minor allele frequencies showed that a weighted score of six SNPs performed as well as the 12 SNP-Score. Thus, to improve cost-efficiency, SNP-Score calculations in a number of replication cohorts were based on genotypes of only the six SNPs with greatest effects on LDL-C shown in bold in Table 1.

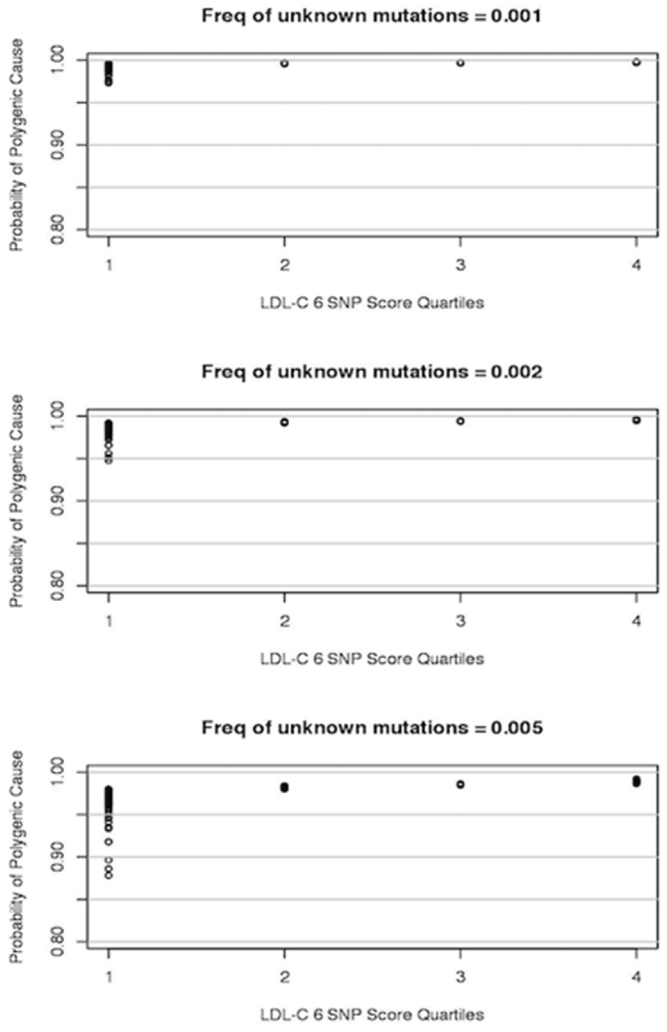

Fig. 1. Probability of having a polygenic cause of hypercholesterolaemia (LDL-C > 4.9 mmol/l) by deciles of SNP-Score, depending on the frequency of undetected mutations (monogenic cause).
(A) When the frequency of unknown mutation is 0.001, (B) when the frequency of unknown mutation is 0.005, (C) when the frequency of unknown mutation is 0.01.

Replication of the SNP-Score effect was carried out in samples from six different countries [17] as shown in Fig. 2. In all samples, the mean score in the FH/M-subjects was higher than in the UK healthy subjects, and overall the effect was highly statistically significant. The highest LDL-C SNP-Score was observed in the two M-hypercholesterolaemic children cohorts (one from the Netherlands and one from Greece), showing that the SNP-Score discriminates well in children as well as adults. Similar data have been obtained in a sample of children with FH from Portugal [18]. 92 FH/M-children were genotyped for the 6 LDL-C genetic risk score SNPs, and the weighted score compared with 1563 healthy Portuguese subjects. Polygenic hypercholesterolaemia was conservatively defined as a score above the top quartile. The FH/M-group had a significantly higher mean (SD) score than the healthy group (0.73 ± 0.17 *vs.* 0.62 ± 0.22, ($p < 0.001$), with over 42% being in the top quartile of the score and only 13% in the bottom quartile. Interestingly, there was no significant difference in mean score between the UK and Portuguese healthy subjects [17]. These data have validated the score in the Portuguese population, and suggests that about half of the FH/M-patients could have polygenic hypercholesterolaemia. Overall, these data suggest that in a child, once a single gene cause for highly elevated LDL-C is ruled out, a polygenic cause is highly likely. A simple spreadsheet is available to calculate the weighted SNP-Score for an individual based on their 12-SNP genotype (Supplementary data).

One of the limitations in the SNP-Score as presented is that all samples are from Caucasian patients, and we currently have no data to allow us to extrapolate the utility of this score to patients from other ethnic backgrounds, where the minor allele frequency will differ considerably, and where the raising effect of the SNPs on LDL-C, although in general are directionally consistent, may not be of similar size [19]. Thus, further data on this is required for the extension of the SNP-Score to different ethnic groups.

4. Estimation of the proportion of FH/M-subjects likely to be polygenic by SNP-Score

In the clinical use of the SNP-Score, we need to estimate the probability that the elevated LDL-C seen in an FH/M-individual can be explained by their weighted SNP-Score. The first estimate needed for this calculation is the underlying rate of undetected monogenic mutations in FH/M-subjects. Accumulating evidence from genotyping and Next Generation Sequencing (NGS) data [20–23] and a recent meta-analysis [24] suggests that, at least in most European populations, around 1/250 people carry an FH-causing mutation. Therefore, the baseline frequency of FH-causing mutations is 0.004. Assuming that we have found 90% of all mutations, the frequency of remaining undetected mutations will be 0.0004. Based on the lack of novel FH causing genes reported to date (e.g. Ref. [25]), this is a reasonable estimate. If we have identified only 75% of all mutations, the frequency of the remaining undetected mutations would be 0.0005, and this seems likely to be the upper limit of undetected mutations. We modelled the likelihood of an individual having an LDL-C >4.9 mmol/l (the FH diagnostic cut-off used by the UK diagnostic criteria) at an undetected mutation frequency of 0.0005. Our analysis [17], shown in Fig. 1, suggests that the probability of a polygenic cause for LDL>4.9 mmol/L in all the assessed FH/M-individuals with a score above the first decile is >95%, which reduces when the frequency of an undetected monogenic cause increases. This suggests that, except for those with a SNP score in decile 1, all other FH/M-subjects have a probability of >90% of a polygenic case explaining their elevated LDL-C (>4.9 mmol/l). In individuals with a clinical diagnosis of FH with a SNP-Score in the lowest decile, it is very unlikely that there is a polygenic cause, and research to identify whether the individuals have a mutation in a yet to be identified gene would be valuable.

A recent small study [26] has used a weighted 10- or 12-SNP score and compared 8 Dutch children with a clinical diagnosis of FH but no causative mutation and 26 of their “affected” or “unaffected” relatives. The overall median 10-SNP allele count of index cases and relatives was not significantly different, but the weighted SNP score was not presented, and a sample this small is very unlikely to result in a statistically significant difference. Although the authors conclude the score is not useful as a diagnostic tool to individually define clinically diagnosed FH patients with polygenic hypercholesterolemia, the study does not use the score in a systematic way to predict the likelihood that a particular child index case has a polygenic or (undetected) monogenic aetiology for their elevated LDL-C phenotype. Although the SNPs used are essentially identical to those used by us [12] [17], comparison between a group of index cases and their relatives is inappropriate, since they are related and will share SNP alleles more often than by chance alone. In our analysis of 22 Dutch children [17] and Fig. 3, the mean weighted score is higher than the UK population sample, supporting our view

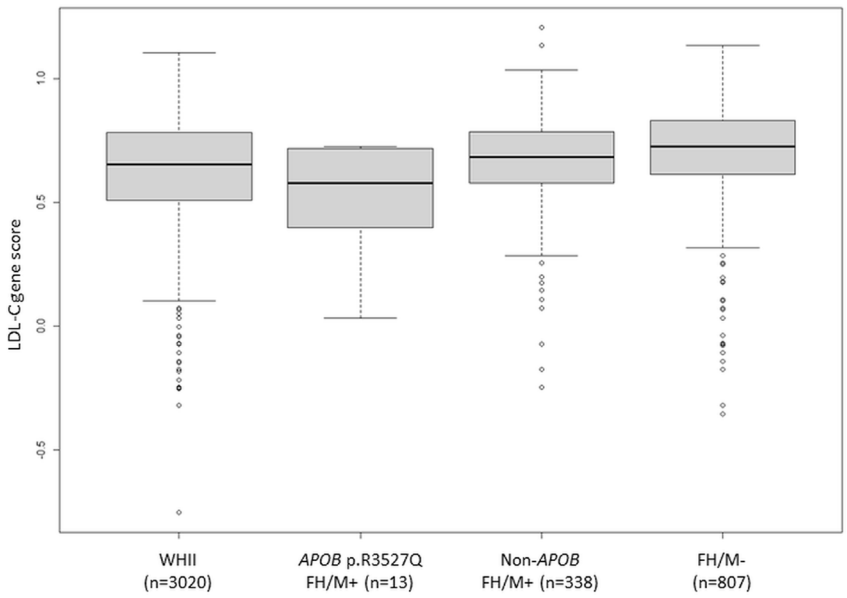

Fig. 2. Boxplot of the LDL-C weighted SNP score in WHII control cohort and patients groups. Data from [10,11].
In the WHII participants, the mean weighted LDL-C gene score was 0.90 ± 0.23). Compared to WHII participants, a significantly higher mean weighted LDL-C gene score was seen in 321 UK FH/M-patients (1.0 ± 0.21; $p = 4.5 \times 10^{-16}$). The score was also higher in 329 UK FH/M+ patients (0.95 ± 0.20; $p = 1.6 \times 10^{-5}$).

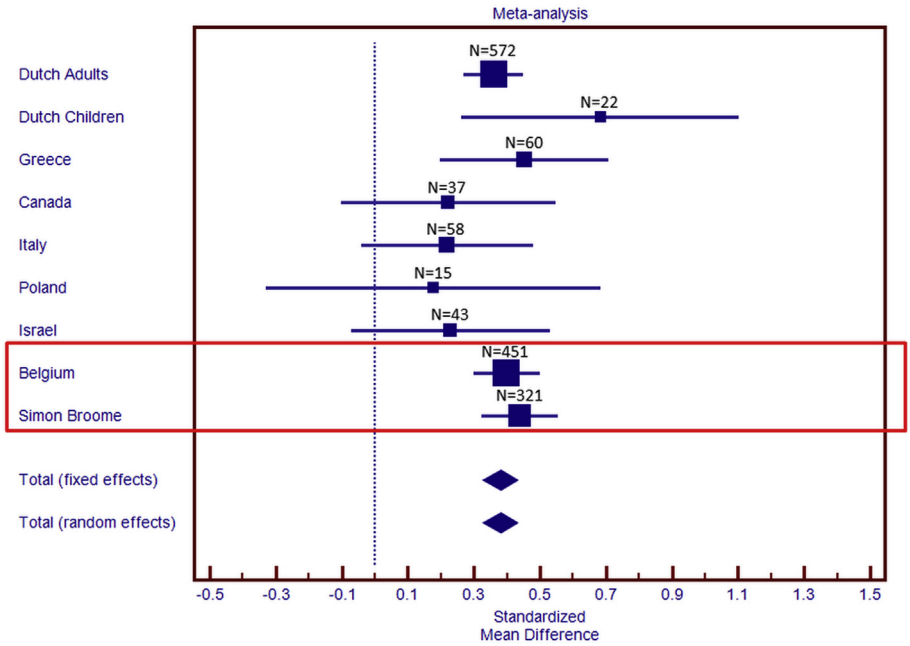

Fig. 3. Meta-analysis of the LDL-C SNP score in nine independent FH mutation negative cohorts in comparison to the WHII population.
Data from [14,15]. Highlighted in the red box are two cohorts studied in the original report [10,11]. The overall SMD was 0.381.

that the weighted mean score is higher in no-mutation children from Holland as well as from other countries.

Although not using a SNP-score, the likelihood of a polygenic aetiology in no-mutation index cases has been examined in 277 relatives of 49 no-mutation index cases from Spain [27]. The authors reported that only 38% of relatives had elevated LDL-C levels (not the 50% expected for a monogenic disorder), and that there was a unimodal (not bimodal) distribution of LDL-C level in relatives, and a lower heritability of LDL-C than in monogenic FH families. Overall, these data are strongly suggestive of a polygenic not monogenic aetiology of the phenotype in these no-mutation families. "In a second study from Spain [28] Next Generation Sequencing (NGS) was used to examine the known FH-causing genes and included the 12-SNPs, in a sample of 129 Spanish patients with Acute Coronary Syndrome under the age of 65 years, and with (untreated) LDL-C over 4.3 mmol/l. While only 8.7% of the patients had an identifiable FH-causing monogenic cause, 29% had an SNP score above the UK 9thth decile described [12]), suggestive of polygenic hypercholesterolaemia. In these subjects, their high SNP score is likely to have resulted in their having elevated LDL-C and early onset heart disease.

5. Variants of unknown significance (VUS)

DNA diagnostic labs have now developed NGS methods whereby all the protein coding and splicing regions of the genome for the known FH genes can be captured and sequenced together as a gene "panel" with high accuracy [29–32], and with the addition of small 'barcoding' sequences attached to the primers used to PCR-amplify the regions of interest, it is now possible to mix the samples from up to 95 individuals (keeping one slot for a no-template control) and analyse them in one run with high accuracy [30]. This economy of scale is helping to drive down prices so that now a full FH diagnostic scan can be completed for around £250, and the data can also be used to review if an individual has a large duplication or deletion of the gene, which occurs in about 5–10% of patients. Other FH phenocopy genes (*APOE*, *LDLRAP1, LIPA, ABCG5/8*) and the polygenic SNP score can also be added to the panel without increasing substantially the cost. These methods produce a large amount of sequence data, requiring statistical and bioinformatics analytical approaches, and this has increased the number of occasions whereby a Variant of Uncertain Significance (VUS) is identified [32]. This creates a diagnostic conundrum which clearly cannot be reported as FH-causing to the clinician or patient, but which requires either *in vitro* molecular assays to examine impact on transcription [33] or splicing [34], or by family studies to see if the variant tracks with high LDL-C levels in the family, while the relatives without the inherited variant have normal levels of LDL-C. However, a number of relatives in a single family, or many families with the same variant, are needed to use co-segregation as a functional proof of disease-causing, and such families are not always available.

It is clearly of great importance to be able to reliably assess the pathogenicity of variants identified in clinical settings, or as incidental findings in genomics projects, in order to allow the appropriate and consistent cascade testing of their relatives. This is not always straightforward in *LDLR/APOB/PCSK9* especially for synonymous and missense variants. For *APOB*, in addition to the two common pathogenic variants (p.(Arg3527Gln) [35] and p(Arg3527Trp) [36]). the ApoB protein is highly polymorphic, with many common and rare variants that do not cause FH (eg Ref. [37])]. Several novel variants in the *APOB* gene have been shown to be FH-causing using *in vitro* assays [38,39]. For *PCSK9* the situation is complicated in that *in silico* prediction algorithms may predict that a missense change is likely to affect function, but cannot distinguish between a gain-of-function, LDL-C raising (possibly FH-causing) variant, and a loss-of-function, LDL-C lowering variant. Additionally, *in silico* analysis is not recommended for complex proteins like *APOB* and *PCSK9*.

In 2015, the Association for Clinical Genetic Science (ACGS) published guidelines for the classification of variants [40], with categories ranging from 1 to 2 (clearly not or unlikely to be pathogenic), to 3 (variants of unknown significance), to 4 and 5 (likely to be or clearly pathogenic). The recently updated *LDLR* variant database with variants classified according to these guidelines may be accessed via: http://databases.lovd.nl/shared/genes/LDLR [41]. Although 93% of *LDLR* variants in the current upgrade of the database have been assigned as pathogenic or likely pathogenic, 7% (115) remain as variants of unknown significance. The American College of Medical Genetics and Genomics has developed an algorithm for variant classification and following this algorithm about half (~1000) of all FH associated variants are considered VUS [37], mainly because of a lack of available data that fits into the specified scoring system.

However, for a VUS in any of the three FH-genes, knowing the LDL SNP-Score may help, since finding a VUS in an individual with a particularly high score would suggest that the variant is less likely to be pathogenic (since the high LDL-C can be explained by the polygenic component), while a low score in an individual with a novel VUS would mean that the variant is more likely to be pathogenic. Such families could then be recruited into co-segregation studies.

6. Identifying new FH genes

The identification of each FH-causing gene has underpinned the development of novel lipid-lowering drugs (*LDLR* and statins, *APOB* and Mipomersen and *PCSK9* and monoclonal antibodies), and the identification of additional FH-causing genes may also reveal novel pathways for which therapeutic agents could be sought. In the UK, the 100,000 genomes project (https://www.genomicsengland.co.uk/the-100000-genomes-project/) has been established to undertake whole genome sequencing in ~70,000 patients (and relatives) with a rare disease, or patients with cancer (and their tumour material). The aim of the project is primarily to create a new genomic medicine service for the NHS, by transforming care pathways for patients. It is hoped that many patients will be offered a diagnosis where there wasn't one before, and the work will help develop best practice for the use of genomics in healthcare, and how best to interpret genomic data to improve patient care. Within 100,000 genomes, patients with a clinical diagnosis of definite FH but with no detectable mutation in *LDLR/APOB/PCSK9* are being recruited. Importantly, only those with a low LDL SNP-Score are being included (for example the five subjects shown as having a score below the 95 percentile bars of the box-whisker plot in Fig. 2), to enhance the chances of finding a new monogenic cause.

7. Clinical utility of a diagnosis of monogenic FH vs polygenic hypercholesterolaemia

There are several lines of evidence to suggest that the extent of atherosclerosis is higher in monogenic compared to polygenic hypercholesterolaemia patients. Many papers report that the prevalence of CHD is higher in groups of mutation positive FH patients compared to those with a clinical diagnosis of FH but where no mutation can be found [35,42,43]. Support for this also comes from the UK Simon Broome register [44], which showed that patients with a clinical diagnosis of definite FH had a higher Standardized Mortality Ratio (SMR) for CHD than those with a clinical diagnosis of possible FH (2.94 vs 2.05). Since a mutation is found in ~80% of DFH patients, the majority of this group will have a monogenic cause. By contrast, a mutation is detected in 25–30% of possible FH patients [7], meaning the majority of this group will have a polygenic cause of their elevated LDL-C. The lower CHD mortality rate in the possible FH patients suggests that the extent of atherosclerosis in polygenic FH is likely to be less.

This elevated risk for CHD in FH patients with a detected mutation has been convincingly confirmed in a population-based analysis [43]. Using NGS for the known FH genes among 20,485 CHD-free individuals, 1386 (6.7%) had LDL-C >4.9 mmol/l, and of these, 24 (1.7%) carried a known FH mutation. Compared with individuals with LDL-C<3.7 mmol/l and no mutation, those with LDL-C >4.9 mmol/l and no FH mutation had a 6-fold higher risk for CHD, but those with both LDL-C >4.9 mmol/l and an FH mutation had a 22-fold higher risk. This risk is likely explained by the substantially higher accumulated 'LDL-C burden' in monogenic FH subjects, since these individuals will have had genetically-determined lifelong high LDL-C.

Finally, we have recently demonstrated [45] that the degree of thickening in the carotid artery, as measured by ultrasound, is considerably greater in a group of monogenic FH patients compared to a group of patients with a polygenic aetiology, even

though total and LDL-C levels were similar. In addition, coronary calcium score was significantly higher in monogenic vs polygenic patients. While all patients with a clinical diagnosis of FH need cholesterol and CHD risk management, the demonstration of higher levels of atherosclerotic burden in the monogenic patients supports recommendations that they warrant intensive LDL-C lowering under the management of a lipid specialist. In some patients this may include treatment with PCSK9 inhibitors in order to achieve LDL-C target values. By contrast, in those who do not have a monogenic cause for their lipid phenotype, estimation of their CHD risk using risk algorithms is appropriate, and they may be able to be managed in general practice. This use of genetic information to risk stratify patients with a clinical diagnosis of FH is a paradigm example of the utility of genetic in Precision Medicine. As NGS becomes cheaper, and the bioinformatics analysis has developed further, this may expand to whole genome sequencing to give an individual a more complete picture of their future risk of disease.

8. Conclusions

There is still additional work that needs to be performed before the SNP score can be fully utilised as a diagnostic tool. The 12-SNP score and basic interpretation of a low, intermediate or high likelihood of a polygenic aetiology has, since mid-2016, been included in DNA diagnostic reports on FH patient samples from the Bristol Laboratory, but we have not audited how either clinicians or patients are using the information. Informal indication is that this influences the decision whether or not to pursue further testing. The UK 2017 NICE Guideline makes a distinction between the management of patients with clinical diagnosis of FH and a monogenic cause and those in the no-mutation group, the majority of whom have a polygenic aetiology, but studies are clearly needed to examine to what extent this information is altering patient management. Information leaflets are needed to help explain the implications of the polygenic aetiology to health care professionals and patients and family members. Family studies should be carried out in index cases with a SNP score for example below the first decile and above the ninth decile. This would determine what proportion of the low score cases shows a bi-modal pattern of LDL-C levels suggestive of an (undetected) monogenic cause, and studies in high score cases would provide an estimate of the proportion of relatives who also have a higher than average score and whose elevated LDL-C puts them at heightened risk of early CHD, which warrants lipid lowering therapy. Larger population studies are needed to define the most appropriate diagnostic gene score cut-offs and to estimate the risk of premature CHD associated with different levels of the score. Finally, studies on non-Caucasians are also essential before the score can be fully implemented as a diagnostic tool.

Conflicts of interest

MF reports speakers' fees from Sanofi. SH is the Medical Director of a UCL spin-out company StoreGene that offers to clinicians genetic testing for patients with familial hypercholesterolaemia. SH Directs the Children's FH Register which is supported by a grant from Pfizer given by the International Atherosclerosis Society. MB has received project grants from Alexion and Regeneron.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.06.006.

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